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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/896,032 | 06/29/2001 | Christoph Seidel | HUBR-1067.3 DIV | 2111 |

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| EXAMINER | |
|---|---|
| BROWN, TIMOTHY M | |
| **ART UNIT** | **PAPER NUMBER** |
| 1648 | |

DATE MAILED: 08/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/896,032 | SEIDEL ET AL. | |
| | Examiner | Art Unit | |
| | Timothy M. Brown | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *02 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *40-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.



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## DETAILED ACTION

This Non-Final Office Action is responsive to the communication mailed August 2, 2005. Claims 40-48 are under examination. Claims 1-39 and 49 have been canceled.

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 2, 2005 has been entered.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 40-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention without undue experimentation.

Undue experimentation is based on an analysis of the following factors: the breadth of the claims; the nature of the invention; the state of the prior art; the level of one of ordinary skill; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.

Here, the specification does not enable the breadth of the claims. The claims are drawn to an immunoassay for detecting HCV antibody comprising contacting a sample with a NS3 polypeptide wherein at least one cysteine of the NS3 polypeptide has been modified. Thus, the claims provide that any combination of the polypeptide's cysteine residues may be modified by deletion, substitution or insertion. These modifications however would have an unpredictable effect on antigenicity. For example, replacing a cysteine with a large heterologous polypeptide would certainly affect the polypeptide's specificity for NS3 antibody. Modifying cysteine residues by point mutation would also have an unpredictable effect as research shows that minor cysteine alterations in antigenic viral proteins can alter specificity. Mutations in the cysteine residues of hepatitis B virus (HBV) surface antigen strongly reduces antibody specificity. (Virol. (1995) 211, 535-543). This is also the case with HBe antigen which shows greatly reduced antigenicity when cysteine is mutated at position 61 (J. Virol. (March 1993) 67, 3, 1315-1321). Modifying any one of the first six cysteines of glycoprotein D causes a complete loss of herpes simplex antibody binding. (J. Virol. (November 1990) 64, 11, 5542-5552). Because the effects of modifying cysteine residues are unpredictable, one skilled in the art would have to turn to the specification in order to improve the specifity of NS3 by cysteine modification. In this regard, the specification provides adequate direction and working examples for (i) NS3 polypeptides modified by covalent attachment of iodoacetate, and (ii) the D26 antigen. However, the modifications that fall outside of this range are not enabled due to the unpredictability noted above. The specification does not point out the specific cysteine changes that improve antigenicity. While the specification indicates that cysteines are preferentially replaced with serine, it does not indicate the specific cysteine residues that can be modified. Thus, one skilled in the art would have to invest in extensive experimentation using site-directed mutagenesis in order to discover which of the invention's NS3 cysteine residues improve antigen function. Based on this lack of direction and the unpredictable effects cysteine modification, one skilled in the art would have to invest undue experimentation in order to make and use the claimed invention.

***Response to Arguments***

The declaration of Dr. Ursula-Henrike Winehues-Thelen does not overcome the enablement rejection of claims 40-48 because it is not commensurate in scope with the claims. The claims are drawn to an immunoassay for detecting HCV antibody comprising contacting a sample with a NS3 polypeptide wherein at least one cysteine of the NS3 polypeptide has been modified. The specification provides that cysteine residues may be modified by covalent bonding, substitution or deletion. The declaration however does not support this range of modifications. Rather, the declaration only shows that the antigenicity of NS3 can be improved by covalent modification with iodoacetate. The declaration does not show that NS3 antigenicity can be improved by substituting serine for any combination of amino acids, including amino acids other than serine. The declaration also fails to show that the other covalent modifications (e.g. N-methyl-maleinimide) improve the antigenicity of NS3. Because the declaration is not commensurate in scope with the claims, the enablement rejection of claims 40-48 is maintained.

Note that the declaration does not establish that the effects of cysteine modification are predictable. The art cited above shows that minor changes in cysteine residues can have very different effects on antigenicity, whether it be improving specifity or destroying it. The declaration in contrast points to a single example (Attachment 3) where all but two cysteine residues of an NS3 polypeptide were altered. This showing does not establish that NS3 antigen would respond to cysteine modifications any differently than the viral antigens in the cited examples. Thus, the declaration fails to establish that the effects of cysteine modification are predicatable.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy M. Brown whose telephone number is (571) 272-0773. The examiner can normally be reached on Monday - Friday, 8am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Timothy M. Brown
Examiner
Art Unit 1648

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SHANON FOLEY
PRIMARY EXAMINER